REMARKS

Status

In this amendment, claims 1, 2, 6-10, 12, 14 and 16 are cancelled without disclaimer or prejudice to prosecution of the claimed subject matter in this or a future application. Claim 4 is amended, and new claims 17-24 are added. The amendments and new claims are supported in the specification. Support for the amendment to Claim 4 is found, *inter alia*, at paragraph [0019]; support for Claims 19 and 20 is found, *inter alia*, at paragraph [0020]; support for Claims 21-23 is found, *inter alia*, at paragraph [0006].

A species election was required in this case. Accordingly, the claims are under examination to the extent they read on the elected species (methods for treatment of Parkinson's Disease). Applicants note that upon allowance of a generic claim, applicant will be entitled to claims to additional species which are written in dependent form or otherwise include all of the limitations of the allowed generic claim. New claims 17-25 read on the elected species.

Claim Rejections Under 35 U.S.C §§ 101 and 112, Second Paragraph

The rejections are moot as to Claims 1, 2, 6-10, 12, 14 and 16, which have been cancelled. Claim 4 has been amended and new claims 17-25 have been added. Applicants believe that amendment and new claims overcome the rejections under Sections 101 and 112, second paragraph.

Claim Rejections Under 35 U.S.C § 112, First Paragraph

The Office states that Zeevalk et al., 2002, shows that that Saclofen, a $GABA_B$ receptor antagonist, was "without effect on the malonate-induced toxicity of straital dopamine neurons in a mouse [*sic*, rat] model of Parkinson's disease." The Office concludes from this that "it would not be predictable that $GABA_B$ receptor antagonists would have any benefit in the treatment of Parkinson's disease." Applicants respectfully disagree that Zeevalk warrants such a conclusion, and submits that one of skill would appreciate that $GABA_B$ receptor antagonists would have benefit in Parkinson's Disease and other conditions.

Nothing in the experiments or results of Zeevalk, et al. are inconsistent with the determination of the present inventors that antagonism of $GABA_B$ receptors increases neurotrophin levels in the CNS, or the expectation that such increases would be beneficial to subjects with Parkinson's Disease. The teachings of Zeevalk, et al., merely

indicate that inhibition of GABA transporter blockade may have a protective effect, that attenuates GABA loss, during malonate-induced striatal damage. However, Zeevalk, et al. do not address the possibility that a $GABA_B$ antagonizing agent may increase neurotrophin levels which increase has a beneficial effect in the treatment of Parkinson's disease. The beneficial effect of increased neurotrophin levels is not dependent upon any protective effect identified in Zeevalk, et al.

The present inventors have surprisingly demonstrated that administration of a $GABA_B$ receptor antagonist increases neurotrophin levels in the CNS. Markedly *decreased* levels of neurotrophins have been observed in the nigrostriatal dopamine regions of Parkinson patients,[1,2] and, as explained below, a considerable body of evidence would lead one of ordinary skill in the art to predict that increased neurotrophin levels in the CNS provide benefit to patients with Parkinson's Disease (PD) and other diseases.

A number of studies in animal models of PD establish that neurotrophins have a beneficial effect. See for example, Bradford et al., 1999, "Neurotrophins in the Pathogenesis and Potential Treatment of Parkinson's disease" *Parkinson's Disease Advanced in Neurology* 80:19-25; and Siegel et al., 2000, "Neurotrophic factors in Alzheimer's and Parkinson's disease brain" *Brain Res Brain Res Rev.* 33:199-227

For example, using the MPTP (methyl-4-phenyl-1,2,3,6-tetrahydropyridine) lesion model, Frim et al showed that administration of BDNF to a MPTP-lesioned rat protects dopaminergic neurons against MPTP-induced toxicity.[3, 4] In similar experiments in mice, MPTP was used to induce depletion of dopaminergic striatal neurons. Three days after

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[1] Howells et al., 2000, "Reduced BDNF mRNA expression in the Parkinson's disease substantia nigra" *Experimental Neurology* 166,127-135.

[2] Nagatsu et al., 2000, "Changes in the cytokines and neurotrophins in Parkinson's disease" *J. Neural Transmission Suppl.* 5,277-290.

[3] The MPTP (methyl-4-phenyl-1,2,3,6-tetrahydropyridine) lesion model is a widely accepted model for PD and is considered to have "direct validity" for assessment of potential neuroprotective agents for this disease. See Ravina et al., 2003, "Neuroprotective agents for clinical trials in Parkinson's disease: a systematic assessment" *Neurology* 60:1234-40. Another widely accepted model for PD model is the 6-OHDA (6-hydroxydopmine) model.

[4] See Frim et al., 1994, "Implanted fibroblasts genetically engineered to produce brain-derived neurotrophic factor prevent 1-methyl-4-phenylpyridinium toxicity to dopaminergic neurons in the rat" *Proc Natl Acad Sci USA* 91:5104-8; also see Siegel et al., 2000, "Neurotrophic factors in Alzheimer's and Parkinson's disease brain" *Brain Res Brain Res Rev.* 33:199-227 at 212.

MPTP administration, NGF was injected into the right cerebral ventricle. Compared to control mice, there was a significant increase of dopamine and homovanillic acid in the striatum, apparently related to a partial restorative effect of NGF on the damaged dopaminergic cells. Thus, administration of NGF to MPTP-lesioned mice produced a beneficial effect on damaged dopaminergic neurons.[5]

In addition, a substantial body of evidence indicates that other drugs that increase CNS neurotrophin levels are useful for treatment of Parkinson's disease.

The drug Selegiline (deprenyl) is used in combination with L-dopa for the treatment of Parkinson's disease. Selegiline enhances NGF protein content in medium from cultured rat cortical astrocytes, and, in *in vivo* experiments, selegiline induced NGF gene expression content in rat cerebral cortex.[6] These results suggest that the induction of NGF by selegiline contributes to the therapeutic benefits of selegiline for the treatment of Parkinson's disease.

Riluzole (2-amino-6-trifluoromethoxy-benzothiazole) is an anticonvulsant drug used for the treatment of amyotrophic lateral sclerosis (ALS) and reported to have neuroprotective effects in animal models of Parkinson's disease. Based on these observations, Mizuta et al.[7] measured the effects of riluzole on the synthesis of NGF, BDNF and GDNF in cultured mouse astrocytes. Treatment with riluzole at 100 µg/ml for 24 h increased the content of NGF, BDNF and GDNF in the culture medium 109-fold, 2-fold, and 3.1-fold over controls, respectively, suggesting the neuroprotective effects of riluzole in neurodegenerative disorders may be mediated by increased neurotrophin synthesis.

Apomorphine, a D_1 D_2 dopamine agonist, is an antiparkinsonian drug. Ohta et al.[8] examined the effects of apomorphine on synthesis of neurotrophic factors in cultured mouse astrocytes. After 24 h incubation with apomorphine, NGF and GDNF content in the culture medium increased to 122-fold and 1.8-fold of the control, respectively (BDNF

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[5] See Garcia et al., 1992, "Ventricular injection of nerve growth factor increases dopamine content in the striata of MPTP-treated mice" *Neurochem Res.* 17:979-82

[6] Semkova et al., 1996, Selegiline enhances NGF synthesis and protects central nervous system neurons from excitotoxic and ischemic damage. *Eur. J. Pharmacol.* 315,19-30.

[7] Mizuta et al., 2001, "Riluzole stimulates nerve growth factor, brain-derived neurotrophic factor and glial cell line derived neurotrophic factor synthesis in cultured mouse astrocytes" *Neuroscience Letters* 310,117-120.

[8] Ohta et al., 2000, "Apomorphine up-regulates NGF and GDNF synthesis in cultured mouse astrocytes" *Biochemical* and *Biophysical Research Communications* 272:18-22.

content did not change significantly). In Parkinson's patients, nigral dopaminergic neurons are progressively depleted, but the surrounding astrocytes remain intact. These results suggest that apomorphine may exert neuroprotective effects by stimulation of NGF and GDNF synthesis in astrocytes, which in turn promote neuronal survival by secreting neurotrophic factors. Similarly, Furukawa et al.[9] showed that dopamine, the active ingredient of levodopa (Ldopa), enhances synthesis and secretion of NGF in cultured mouse astrocytes.

Memantine, a noncompetitive n-methyl-D-aspartate receptor antagonist, is used clinically as a neuroprotective agent to treat Parkinson's diseases. Marvanova et al.[10] showed that Memantine at clinically relevant doses markedly increases BDNF mRNA and BDNF protein levels in several regions of the rat brain. These results indicate that the neuroprotective properties of memantine could be mediated by the increased of BDNF in the brain (in the limbic cortex but also in doparninergic brain areas such as the ventral tegrnental area the substantia nigra and the thalamus).

Administration of adenosine A_{2A} receptor antagonists alleviates parkinsonian symptoms without provoking dyskinesia in MPTP-treated monkeys (Kanda et al.[11]). Ikeda et al.[12] have shown that administration of A_{2A} receptor antagonists protected against the loss of nigral dopaminergic neural cells induced by 6-hydroxydopamine in rats and prevented the functional loss of dopaminergic nerve terminals in the striatum and the ensuing gliosis caused by MPTP in mice. Previously, Heese et al.[13] demonstrated that A_{2A} antagonists increased NGF expression and release in microglial cells. Thus, the mechanism by which A_{2A} receptor antagonists protect dopaminergic neurons from the

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9 Furukawa et al., 1993, "Alkylcatechols regulate NGF gene expression in astroglial cells via both protein kinase C and cAMP-independent mechanisms" *J. Neurosci. Res.* 35,522-529.

10 Marvanova et al., 2001, "The neuroprotective agent memantine induces brain-derived neurotrophic factor and trkB receptor expression in rat brain" *Molecular and Cellular Neuroscience* 18:247-258.

11 Kanda et al., 1998, "Adenosine A_{2A} antagonist: a novel antiparkinsonian agent that does not provoke dyskinesia in parkinsonian monkeys" *Annales* of *Neurology* 43:507-513.

12 Ikeda et al., 2002, "Neuroprotection by adenosine AZA receptor blockade in experimental models of Parkinson's disease" *J. Neurochemistry* 80:262-70.

13 Heese et al., 1997, "Nerve growth factor (NGF) expression in rat microglia is induced by adenosine A_{2A} receptors" *Neuroscience Letters* 231:83-86.

excitotoxic action of 6-hydroxydopamine and MPTP may be in part mediated by an increase synthesis and release of NGF.

Parkinson's Disease is a debilitating condition for which new therapies are desperately needed. The present inventors' surprising discovery that antagonism of $GABA_B$ receptors increases CNS neurotrophin levels provides an important new therapeutic approach to treatment of Parkinson's Disease. Substantial data, of which only a portion is discussed above, provide an expectation that increases in CNS neurotrophin levels provide benefit in Parkinson's and other diseases.

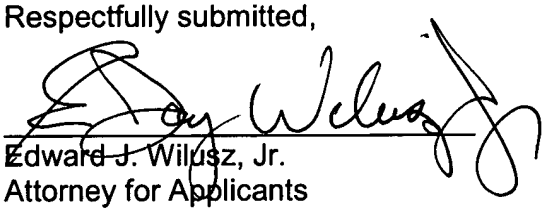
Based on the foregoing the Applicants respectfully request that the Examiner withdraw the rejections under the first paragraph of 35 U.S.C. § 112.

Claim Rejections Under 35 U.S.C § 102(b)

The rejection of the claims under §102(b) is moot in view of the amendment of the claims. Therefore the Applicants respectfully request that the Examiner withdraw the rejections based thereon.

The Applicants believe that the application is now in condition for allowance and respectfully request early notice to that effect. If it will advance prosecution of the Application the Examiner is urged to contact the Applicants' undersigned counsel at the telephone number listed below.

Respectfully submitted,



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